II. The objection to the specification should be withdrawn.

The Examiner objected to the specification for failure to recite the specifics of the deposited material including the date of deposit, the complete name and address of the depository, and the accession number. The specification has been amended to recite each of the elements outlined by the Examiner. Accordingly, Applicant's respectfully request withdrawal of the Examiner's objection to the specification.

III. The rejection of claims 1-5, 7-9, 11-37 and 40 under the judicially created doctrine of obvious-type double patenting, should be withdrawn.

The Examiner rejected claims 1-5, 7-9, 11-37 and 40 under the judicially created doctrine of obvious-type double patenting as being unpatentable over claims 8-13 of U.S. Patent No. 6,361,946 (hereinafter "the '946 patent").

Applicants acknowledge the possibility of filing a Terminal Disclaimer but consider such disclaimer premature at this time becasue the scope and language of the claims that will ultimately be allowed, with the exception of the double patenting issue, is unclear. Applicants respectfully request the requirement for the Terminal Disclaimer be deferred until the scope and language of allowable claims has been settled.

IV. The rejection of claims 5, 7-9, and 11-18 under 35 U.S.C. 112, first paragraph, should be withdrawn.

The Examiner rejected claims 5, 7-9, and 11-18 under 35 U.S.C. 112, first paragraph, for alleging that the specification fails to provide "support or guidance to determine what patient would be in need of modulation of Flt4." The Applicants thank the examiner for clarifying the reason for the rejection, and respectfully traverse it.

The application teaches that VEGF-C as taught in the application is a ligand for the Flt4 (VEGFR-3) receptor. (See, e.g., page 5, lines 12-13.) Thus, the teachings related to both Flt4 and VEGF-C provide guidance to identification of patients that will benefit from modulation of Flt4. The specification teaches that Flt4 is expressed on (and becomes largely restricted to) lymphatic vessels (see p. 4, line

21, to p. 5, line 2), and that the patients in need of modulation of their lymphatics are candidates to receive the Flt4 ligand taught in the application:

> The biological effects of VEGF-C on lymphatic endothelia indicate *in vivo* uses for polypeptides of the invention for stimulating lymphangiogenesis (e.g., to promote re-growth or permeability of lymphatic vessels in, for example, organ transplant patients; to mitigate the loss of axillary lymphatic vessels following surgical interventions in the treatment of cancer (e.g., breast cancer); to treat aplasia of the lymphatic vessels or lymphatic obstructions) and for inhibiting it (e.g., to treat lymphangiomas). Additional *in vivo* uses for polypeptides of the invention include the treatment or prevention of inflammation, edema, elephantiasis, and Milroy's disease.
>
> (Page 21, lines 3-10. See also Example 29 on page 82, lines 14-19)

Thus, the specification as filed identifies a variety of patients that will benefit from Flt4 modulation in contexts related to the lymphatics..

In addition, the application teaches that other patients will benefit by modulation of Flt4 for the purposes of affecting white blood cells. For example, the application teaches use of the Flt4 ligand VEGF-C to stimulate myelopoiesis in a mammalian subject in need of modulation of myelopoiesis. (Page 22, last paragraph.) These teachings are supported in part by the teachings in Example 36 that a population of CD34+ progenitor cells express Flt4 (VEGFR-3). (See, e.g., p. 102, lines 14-21.)

Taken together, these and other teachings in the specification provide ample support for identifying patients in need of modulation of Flt4 activity, as recited in the claims. Accordingly, the rejection of claims 5, 7-9, and 11-18 under 35 U.S.C. 112, first paragraph, should be withdrawn.

V. The rejection of claim 22 under 35 U.S.C. 112, first paragraph, should be withdrawn.

Claim 22 was rejected under 35 U.S.C. 112, first paragraph, for allegedly containing subject matter that was not adequately described in the specification to enable one skilled in the art to make and/or use the invention. The

Examiner states that the mere referral to the deposit of Plasmid FLT4-L is insufficient assurance that all of the conditions of 37 CFR 1.801 through 1.809 have been met.

In response, the Applicants have filed a Budapest Treaty Declaration, attached as Appendix D hereto. This declaration was previously filed in related U.S. Patent Application Serial No. 08/585,895, now U.S. Patent No. 6,245,530. This declaration, which pertains to identical deposited material as in the instant application, satisfies the requirements of 37 CFR 1.801 through 1.809. Accordingly, the Applicants respectfully request that the rejection of claim 22 under 35 U.S.C. 112, first paragraph, be withdrawn.

VI. The rejection of claims 19-27 under 35 U.S.C. 112, first paragraph, should be withdrawn.

The Examiner rejected claims 19-27 under 35 U.S.C. 112, first paragraph, alleging that the claims encompass gene therapy, yet the specification, while being enabling for a method of stimulating endothelial cell growth comprising administering a polypeptide comprising the amino acid sequence of SEQ ID NO: 8 and variants thereof, does not reasonably provide enablement for gene therapy using nucleic acids encoding these polypeptide fragments. The Applicants respectfully traverse.

The first basis for rejection alleges that there are no conditions disclosed to be treated. As explained above in response to the rejection of claim 5, the application contains abundant teachings (with evidence) concerning the biological roles of VEGF-C and its receptor Flt4 in certain disease states and conditions to be treated.

The examiner further alleged that the specification and prior art provide insufficient guidance as to the vectors, promoters, transcriptional elements, and administration methods that are necessary for this type of therapy. To the contrary, the specification provides guidance to use expression wherein nucleic acids of the invention are operatively connected to appropriate promoters and other control sequences that regulate transcription and/or subsequent translation, such that appropriate prokaryotic or eukaryotic host cells transformed or transfected with the vectors are capable of expressing the polypeptide encoded thereby (e.g., the VEGF-C,

VEGF-C fragment, VEGF-C variant, or VEGF-C analog encoded thereby). (See, e.g., p. 16, line 29, to p. 17, line 9.)

The examiner cited no evidence supporting the contention as to the inadequacy of the state of the prior art (notwithstanding the fact that the Patent Office has the burden of supporting rejections). Signficantly, the prior art at the time that the application was filed (first claimed priority date in 1995) contained abundant teachings concerning gene therapy vectors, promoters, transcriptional elements, and administration methods. A search of the Patent Office's own database identifies numerous issued patents, filed before August, 1995, that are directed to adenoviral, adeno-associated viral, retroviral, and other gene therapy vectors, and that, presumptively under the law, were enabled as of their filing dates for whatever gene therapy materials and methods were claimed therein. Likewise, a search of literature databases identifies numerous articles, published before August 1995, describing *in vivo* gene therapy studies. It is axiomatic that a patent application need not disclose what is well known in the art, *In re Wands*, 8 USPQ2d 1400, 1402 (Fed. Cir. 1988), and there was abundant art pertaining to gene therapy materials and methods at the time that the present application was filed. Thus, the allegation that one skilled in the art was not enabled by the application and prior art to select suitable vectors, promoters. etc., is contrary to the weight of available evidence.

The Patent Office also alleged that the specification lacks working examples. To the contrary, Example 29 of the application describes the *in vivo* expression of human VEGF-C protein in mice using the human K14 skin-specific (keratin) promoter. The example showed that the mice were viable and that the intentionally over-expressed VEGF-C in the skin caused proliferation of lymphatic vessels in the skin and also, a myelopoietic effect in the blood (Example 36). This example demonstrates that VEGF-C can be introduced in the form of a polynucleotide *in vivo* to exert lymphangiogenic and myelopoietic effects. It directly refutes the allegation that there is insufficient guidance or evidence for using polynucleotides *in vivo*.

Thus, the teachings in the application and state of the gene therapy prior art establish that VEGF-C polynucleotides can be administered efficaciously *in vivo*. For these reasons, the rejection under Section 112 should be withdrawn.

CONCLUSION

For the foregoing reasons, reconsideration and withdrawal of all rejections and objections is requested. To expedite allowance, the applicants request a telephonic interview to attempt to resolve any issues that remain unresolved by this amendment.

This amendment is timely filed with a petition and fee for a two month extension of time to extend the period for response until February 28, 2003. The Patent Office is authorized to charge any other necessary fees associated with this submission to Deposit Account No. 13-2855.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6357
(312) 474-6300
(312) 474-0448 (Telefacsimile)

Dated: February 28, 2003

By: _____
David A. Gass
Registration No. 38,153

APPENDIX A

Marked-up Version of the Specification

At page 44, lines 1-3"

Plasmid pFLT4-L, containing the 2.1 kb human cDNA clone in pcDNAI vector, has been deposited with the American Type Culture Collection, [12301 Parklawn Drive, Rockville, MD 20852] 10801 University Boulevard, Manassas, VA 20110-2209, on July 24, 1995, as accession number 97231.

At page 11, lines 9-12:

Deposit of Biological Materials: Plasmid FLT4-L has been deposited with the American Type Culture Collection (ATCC), [12301 Parklawn Dr., Rockville MD 20952 (USA)] 10801 University Boulevard, Manassas, VA 20110-2209, pursuant to the provisions of the Budapest Treaty, and has been assigned a deposit date of 24 July 1995 and ATCC accession number 97231.

APPENDIX C

Marked-up Version of the Claims

13. A method according to claim 5, wherein the polypeptide is [purifyable]purifiable from conditioned media from a PC-3 prostatic adenocarcinoma cell line, said cell line having ATCC Accession Number CRL 1435, using an affinity purification procedure wherein the affinity purification matrix comprises a polypeptide comprising the extracellular domain of Flt4 receptor tyrosine kinase.

APPENDIX D

Budapest Treaty Declaration